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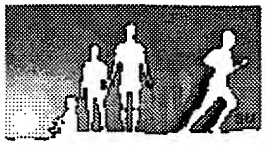

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Betaine:homocysteine methyltransferase--a new assay for the liver enzyme and its absence from human skin fibroblasts and peripheral blood lymphocytes.

Wang JA; Dudman NP; Lynch J; Wilcken DE Department of Cardiovascular Medicine, Prince Henry Hospital, University of New South Wales, Sydney, Australia. Clin Chim Acta (NETHERLANDS) Dec 31 1991, 204 (1-3) p239-49,

Chronic elevation of plasma homocysteine is associated with increased atherogenesis and thrombosis, and can be lowered by betaine (N,N,N-trimethylglycine) treatment which is thought to stimulate activity of the enzyme betaine:homocysteine methyltransferase. We have developed a new assay for this enzyme, in which the products of the enzyme-catalysed reaction between betaine and homocysteine are oxidised by performic acid before being separated and quantified by amino acid analysis. This assay confirmed that human liver contains abundant betaine:homocysteine methyltransferase (33.4 nmol/h/mg protein at 37 degrees C, pH 7.4). Chicken and lamb livers also contain the enzyme, with respective activities of 50.4 and 6.2 nmol/h/mg protein. However, phytohaemagglutinin-stimulated human peripheral blood lymphocytes and cultured human skin fibroblasts contained no detectable betaine:homocysteine methyltransferase (less than 1.4 nmol/h/mg protein), even after cells were pre-cultured in media designed to stimulate production of the enzyme. The results emphasize the importance of the liver in mediating the lowering of elevated circulating homocysteine by betaine.

TOP

Dimethylglycine and chemically related amines tested for mutagenicity under potential

nitrosation conditions.

Hoorn AJ Hazleton Biotechnologies, Veenendaal, The Netherlands. Mutat Res (NETHERLANDS) Apr 1989, 222 (4) p343-50, ISSN 0027-5107

Dimethylglycine (DMG) and the chemically related amino acids glycine, sarcosine (monomethylglycine) and betaine (trimethylglycine) were tested in Salmonella typhimurium strain TA100 after treatment with sodium nitrite under acidic conditions using a modified Ames Salmonella/microsome assay as reported by Colman et al. (1980). The increase in the number of revertants observed both with and without metabolic activation was also induced in the control mixtures without adding the amines. From the subsequent testing of the individual components of the mixtures, we concluded that non-consumed nitrite was responsible for the mutagenic responses observed in the different reaction mixtures, and not the amines themselves. There were no consistent indications of mutagenic activity of the DMG test mixture as compared to the control mixture which exhibited both consistent mutagenic activity and a toxic effect which was not increased by the addition of DMG. In fact, DMG seemed to decrease the toxicity of the control reaction solution to the Salmonella which was clearly observed at the higher doses. DMG cannot be considered mutagenic under the test conditions employed. The same can be said of the other amino acids as well.

TOP

[Cholagogic effect of trimethylglycine in normal animals of different ages and in experimental atherosclerosis]

Zhelchegonnyi effekt trimetilglitsina u zhivotnykh raznogo vozrasta v norme i pri eksperimental'nom ateroskleroze. Zapadniuk VI; Panteleimonova TN Biull Eksp Biol Med (USSR) Jul 1987, 104 (7) p30-2, ISSN 0365-9615

Trimethylglycine at a dose of 1.5 g/kg was found to produce marked bile secretory effect in young and old rats. In rabbits with experimental atherosclerosis, trimethylglycine increased the content of biliary acids in the bile and normalized the indexes of lipid metabolism in the blood serum. Apparently, the effect on cholesterol transformation into biliary acids and its excretion with the bile is one of the mechanisms of anti-atherosclerotic action of trimethylglycine.

TOP

[Corrective effect of trimethylglycine on the nicotinamide coenzyme and adenine nucleotide content of the tissues in experimental

atherosclerosis]

Korrigiruiushchee vliianie trimetilglitsina na soderzhanie nikotinamidnykh kofermentov i adeninnukleotidov v tkaniakh pri eksperimental'nom ateroskleroze. Zapadniuk VI; Chekman IS; Panteleimonova TN; Tumanov VA Farmakol Toksikol (USSR) Jul-Aug 1986, 49 (4) p71-3, ISSN 0014-8318

Experiments on adult rabbits with experimental atherosclerosis induced by cholesterol (0.25 g/kg for 90 days) showed that chronic administration of trimethylglycine (1.5 g/kg for 30 days) prevented a decrease of the liver and myocardium content of nicotinamide coenzymes and adenine nucleotides.

TOP

Homocystinuria due to cystathionine beta-synthase deficiency--the effects of betaine treatment in pyridoxine-responsive patients.

Wilcken DE; Dudman NP; Tyrrell PA Metabolism (UNITED STATES) Dec 1985, 34 (12) p1115-21, ISSN 0026-0495

Homocystinuria due to cystathionine beta-synthase deficiency may be responsive to pyridoxine, a precursor of the cofactor pyridoxal phosphate, and the amount of residual enzyme activity present is the probable determinant of this. In six treated pyridoxine-responsive patients whose biochemical control of fasting plasma amino acid levels appeared optimal, we assessed the effects on plasma amino acids of standard oral methionine loads (4g/m2 of body area) before and after adding betaine (trimethylglycine) 6 g/d, to the treatment regimen of pyridoxine and folic acid. Our aim was to define the capacity of these patients to metabolize methionine and to determine whether betaine would effect a reduction in postload homocysteine levels. During the 24 hours after the methionine challenge all patients had higher plasma methionine and homocysteine and lower cysteine than did 17 normal subjects. After betaine these homocysteine responses were reduced to near normal, and there was a trend toward increased methionine. There was a direct correlation between premethionine fasting homocysteine and mean homocysteine responses during the 24 hours following the methionine load, both before ($r = 0.79$) and after betaine ($r = 0.71$). Betaine also increased plasma cysteine levels in patients with the more severe biochemical abnormalities. After betaine there were modest increases in plasma serine (mean increase 25%; P less than 0.025). Since the vascular complications of homocystinuria are related to increased plasma homocysteine, betaine therapy may reduce this risk in patients receiving a standard pyridoxine and folic acid regimen in whom there are abnormal homocysteine responses after a standard methionine load.

TOP

Prevention of strychnine-induced seizures and death by the N-methylated glycine derivatives betaine, dimethylglycine and sarcosine.

Freed WJ Pharmacol Biochem Behav (UNITED STATES) Apr 1985, 22 (4) p641-3, ISSN 0091-3057 Journal Code: P3Q

Betaine (N,N,N-trimethylglycine) and N,N-dimethylglycine have been reported to have anticonvulsant properties in animals. The purpose of the present study was to determine whether these compounds can antagonize strychnine-induced seizures when administered intraperitoneally and to compare their effects with those of sarcosine (N-methylglycine) and glycine. Betaine, N,N-dimethylglycine and sarcosine were equipotent in decreasing the incidence of seizures and death, causing a 38 to 72 percent decrease in the incidence of seizures and death at a dosage of 5 mmole/kg. Glycine had no effect. Thus anticonvulsant activity is conferred to glycine by a single N-methylation.

TOP

[Effect of trimethylglycine on lipid metabolism in experimental atherosclerosis in rabbits]

Vliianie trimetilglitsina na lipidnyi obmen pri eksperimental'nom ateroskleroze u krolikov. Panteleimonova TN; Zapadniuk VI Farmakol Toksikol (USSR) Jul-Aug 1983, 46 (4) p83-5, ISSN 0014-8318

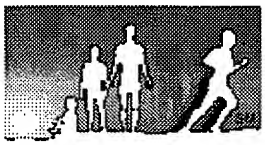
It has been shown in adult rabbits aged 8 months with experimental cholesterol atherosclerosis that administration of trimethylglycinee in a dose of 0.5 g/kg reduces the elevated content of total and ester-bound cholesterol, beta-lipoproteins, total lipids in the blood serum and that of total cholesterol and triglycerides in the liver. Little toxicity and high efficacy of trimethylglycin in experimental atherosclerosis make this compound prospective in the light of its use as an antisclerotic agent.

TOP

Amelioration of ethionine toxicity in the chick.

Lowry KR; Baker DH Department of Animal Sciences, University of Illinois, Urbana 61801. Poult Sci (UNITED STATES) Jun 1987, 66 (6) p1028-32, ISSN 0032-5791

Several chick bioassays were conducted to evaluate means of ameliorating ethionine toxicity. Supplementing a corn-soy diet marginally deficient in sulfur amino acids (methionine + cystine) with .075% D,L-ethionine reduced



weight gain in 8-day-old chicks by 70% compared to gains of unsupplemented controls. Dietary addition of .50% DL-methionine prevented reduction in weight gain and feed intake resulting from ethionine supplementation whereas feeding supplemental L-cystine was without effect. Supplementation of the ethionine-containing diet with either choline or betaine ameliorated the growth depression, although neither compound was able to completely overcome the toxic effects of ethionine. Dietary ethionine did not affect plasma levels of free methionine or cystine but did increase plasma free glycine 6-fold. Dietary addition of .50% DL-methionine caused normalization of plasma glycine levels whereas it elevated plasma methionine concentration. Although results suggested the possibility of ethionine-induced serine or threonine deficiency, dietary additions of .75% L-serine or .75% L-threonine failed to improve chick weight gain. These studies suggest that ethionine, in addition to affecting transsulfuration and transmethylation activity may exert specific effects on certain amino acids in tissue pools.

TOP

Effects of betaine on seizures in the rat.

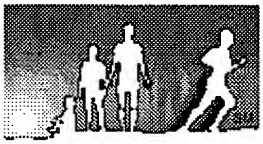
Ghoz EH; Freed WJ Pharmacol Biochem Behav (UNITED STATES) Apr 1985, 22 (4) p635-40, ISSN 0091-3057 Journal Code: P3Q

The ability of betaine to block homocysteine, pentylenetetrazol, and electroshock induced seizures in mice has previously been observed. In this study, betaine administered IP and intraventricularly to rats blocked pentylenetetrazol-induced seizures, but IP betaine did not block audiogenic seizures. Intraventricular betaine was about 1000-fold more potent than IP betaine in blocking PTZ-induced seizures. Glycine, a component of the betaine molecule, was ineffective. It is concluded that betaine has an appreciable but selective effect in controlling experimental seizures in rats. This effect is mediated directly by the brain, and is not due to metabolism of betaine to glycine.

Serum betaine, N,N-dimethylglycine and N-methylglycine levels in patients with cobalamin and folate deficiency and related inborn errors of metabolism

Allen R.H.; Stabler S.P.; Lindenbaum J. Division of Hematology, Colorado Univ. Health Sciences Ctr., Campus Box B170, 4200 E Ninth Ave, Denver, CO 80262 USA METAB. CLIN. EXP. (USA) , 1993, 42/11 (1448-1460)

Homocysteine and 5-CH3-tetrahydrofolate (5-CH3-THF) are converted to methionine and THF by the CH3-cobalamin (CH3-Cbl)-dependent enzyme



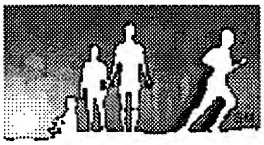
methionine synthase. Serum homocysteine levels are elevated in more than 95% of patients with Cbl or folate deficiency and in patients with inborn errors involving the synthesis of 5-CH3-THF or CH3-Cbl. Homocysteine and betaine are converted to methionine and N,N-dimethylglycine by betaine-homocysteine methyltransferase. It requires neither Cbl nor folate, although N,N- dimethylglycine is converted to N-methylglycine and then to glycine in reactions that both involve the formation of 5,10-CH2-THF from THF. Large amounts of betaine are often given orally to patients with inborn errors, even though little is known about its metabolism in normal subjects or these patients. Thus we developed new gas chromatographic-mass spectrometric assays for serum betaine, N,N-dimethylglycine, and N-methylglycine. In 60 blood donors, we found ranges for normal serum of 17.6 to 73.3, 1.42 to 5.27, and 0.60 to 2.67 micromol/L for the three metabolites, respectively, which were normal in the majority of 50 patients with Cbl deficiency, none of whom had increased levels of N-methylglycine. In 25 patients with folate deficiency, serum betaine level was normal in most, but 76% and 60% had elevations of N,N-dimethylglycine and N-methylglycine levels that ranged as high as 343 and 43.2 micromol/L, respectively. All of seven patients on betaine therapy for inborn errors had high values for betaine (167 to 3,900 micromol/L), N,N- dimethylglycine (15.1 to 250 micromol/L), and N-methylglycine (2.93 to 49.3 micromol/L). Serum total homocysteine levels remained very high at 47.2 to 156 micromol/L (normal, 5.4 to 16.2). In patients with cbl C and cbl D mutations, methionine levels remained low or low-normal at 8.3 to 15.6 micromol/L (normal, 13.3 to 42.7) despite betaine treatment. We conclude that (1) betaine levels are maintained in most patients with Cbl and folate deficiency; (2) levels of N,N-dimethylglycine and N-methylglycine are increased in most patients with folate deficiency; and (3) betaine therapy is relatively ineffective in patients with defective synthesis of CH3-Cbl.

TOP

Characterization of betaine efflux from rat liver mitochondria

Porter R.K.; Scott J.M.; Brand M.D. Department of Biochemistry, University of Cambridge, Cambridge CB2 1QW United Kingdom
BIOCHIM. BIOPHYS. ACTA BIOENERG. (Netherlands) , 1993, 1141/2-3 (269-274)

In order to investigate the control of endogenous betaine supply to the cytoplasmic enzyme betaine-homocysteine methyltransferase, it was necessary to understand how betaine synthesized within the mitochondrial matrix is transported across the mitochondrial inner membrane. Mitochondria were loaded with radiolabelled betaine and efflux was measured in a medium at physiological ionic strength. Efflux of radiolabelled betaine occurred continuously within time. The efflux rate was unaffected by the presence or absence of a source of energy except at high membrane potentials, where betaine efflux rate increased 2-3 fold. Titration



of the membrane potential demonstrated a non-ohmic relationship between betaine efflux rate and membrane potential. The rate of betaine efflux was proportional to the matrix betaine concentration up to 9 mM. Efflux was unaffected by addition of analogues of betaine and known mitochondrial transport inhibitors. N-Ethylmaleimide did inhibit efflux by 50%, but evidence suggested that the effect was non-specific. The lack of saturability or other evidence for a transport system suggests that betaine escapes from mitochondria by simple diffusion. The relative diffusion rates of glycine, sarcosine, dimethylglycine and betaine suggest that increasing the degree of N-methylation lowers diffusion rate.

TOP

Metabolism of S-adenosylmethionine in rat hepatocytes: Transfer of methyl group from S-adenosylmethionine by methyltransferase reactions

Tsukada K.; Abe T.; Kuwahata T.; Mitsui K. Department of Pathological Biochemistry, Medical Research Institute, Tokyo Medical and Dental University, Tokyo 101 JAPAN LIFE SCI. (USA) , 1985, 37/7 (665-672)

Treatment of rats with a methionine diet leads not only to a marked increase of S-adenosylmethionine synthetase in liver, but also to the increase of glycine, guanidoacetate and betaine-homocysteine methyltransferases. The activity of tRNA methyltransferase decreased with the increased amounts of methionine in the diets. However, the activities of phospholipids and S-adenosylmethionine-homocysteine methyltransferases did not show any significant change. When hepatocarcinogenesis induced by 2-fluorenylacetamide progresses, the activities of glycine and guandioacetate methyltransferases in rat liver decreased, and could not be detected in tumorous area 8 months after treatment. The levels of S-adenosylmethionine in the liver also decreased to levels of one-fifth of control animals at 8 months. The uptake and metabolism of (methyl-sup 3H)-methionine and -S-adenosylmethionine have been investigated by in vivo and isolated hepatocytes. The uptake of methionine and transfer of methyl group to phospholipid in the cells by methionine were remarkably higher than those by S-adenosylmethionine. The results indicate that phospholipids in hepatocytes accept the methyl group from S-adenosylmethionine immediately, when it is synthesized from methionine, before mixing its pool in the cells.

TOP

Effect of cobalamin inactivation on folate-dependent transformylases involved in purine

synthesis in rats

Deacon R.; Perry J.; Lumb M.; Chanarin I. Haematology Section, M.R.C. Clinical Research Centre, Northwick Park Hospital, Harrow, Middx. HA1 3UJ UNITED KINGDOM BIOCHEM. J. (ENGLAND) , 1985, 227/1 (67-71)

Nsub 2O oxidizes and inactivates cob(I)alamin, and animals exposed in this way serve as models for cobalamin 'deficiency'. Such animals show a fall in activity of glycinamide ribotide transformylase and a rise in that of 5-amino-4-imidazolecarboxamide ribotide transformylase. The fall in glycinamide ribotide transformylase activity was prevented by parenteral 5'-methylthioadenosine derived from methionine. Methylthioadenosine in turn is converted into formate. Activity of glycinamide ribotide transformylase recovers after 7 days despite continued Nsub 2O inhalation, and this is probably related to restoration of methionine synthesis by induction of betaine:homocysteine transmethylase.

TOP

Labile methyl group balances in the human: The role of sarcosine

Mudd S.H.; Ebert M.H.; Scriver C.R. Lab. Gen. Comp. Biochem., Nat. Inst. Ment. Hlth, Bethesda, Md. 20014 USA METAB. CLIN. EXP. (USA) , 1980, 29/8 (707-720)

Estimates of the daily rate of methionine utilization by adult humans, published previously, were underestimated because available data did not permit quantitative assessment of the rate at which the methyl moiety of methionine is oxidized. The present paper reports efforts to measure the rate of oxidation of methionine methyl by the two pathways that proceed through the intermediate N-methylglycine (sarcosine). Two sarcosinemic, sarcosinuric patients, proven or presumed to have specific genetic defects in the sarcosine-oxidizing system, were studied while maintained on constant diets containing differing amounts of methionine, choline (or choline derivatives), and glycine. The steady-state excretions of sacrosine, creatinine, creatine, and a number of other materials were determined. The results obtained suggest that sacrosine is formed in two ways: (1) In an amount equivalent to the dietary intake of choline (or choline derivative)- this pathway would make a net positive contribution to the methionine-methyl pool due to the transfer of a methyl group from betaine to homocysteine; and (2) By processes requiring net consumption of methionine methyl. For the single patient for whom reasonably complete data were attained, it appears that 2 such processes may be occurring. One proceeds at a rate (approximately 2 mmole/24 hr) that changed little as total intake of labile methyl groups was altered. The second became prominent (and accounted for the bulk of the incremental intake of labile methyl groups) when this intake exceeded the combined amounts required for the

synthesis of creatine (10.2 mmole/24 hr), other transmethylation reactions (1.4 mmole/24 hr), polyamine synthesis (0.5 mmole/24 hr), and the 'basal' process of sarcosine formation just mentioned (2 mmole/24 hr). It is possible that such 'basal' sarcosine formation is due chiefly to endogenous choline synthesis, balanced by degradation, whereas the more responsive process of sarcosine formation may be due chiefly to methylation of glycine. Together with available data, these new data on methionine consumption due to sarcosine formation permit calculation of a turnover time for S-adenosylmethionine in human liver (no more than 3.5-7 min), as well as upward revision of previous minimal estimates of the rate of methylneogenesis, the number of times the average homocysteinyl moiety cycles between methionine and homocysteine during its passage through the body, and the partitioning of homocysteine between the remethylation and the transsulfuration pathways.

TOP

Changes in plasma glucose and liver glycogen following the administration of gluconeogenic precursors to the starving fowl

Davison T.F.; Langslow D.R. Houghton Poultry Res. Stat., Houghton, Huntingdon UNITED KINGDOM COMP.BIOCHEM.PHYSIOL. (ENGLAND) , 1975, 52/4a (645-649)

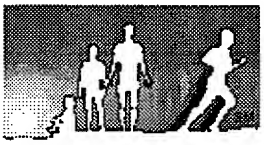
When 6 week old chickens were starved changes in plasma metabolites indicated that gluconeogenesis was well established by 48 hr. The ability to induce hyperglycaemia followed the series lactate > glycerol > pyruvate. The gluconeogenic activity of amino acids was alanine > glycine > aspartate > serine > glutamate > arginine. Lysine and succinate had no gluconeogenic activity. Only serine stimulated an increase in liver glycogen stores.

TOP

Effect of exogenous proline, betaine, and carnitine on growth of Listeria monocytogenes in a minimal medium

Beumer R.R.; Te Giffel M.C.; Cox L.J.; Rombouts F.M.; Abee T. Laboratory of Food Microbiology, Agricultural University, Bomenweg 2, 6703 HD Wageningen Netherlands APPL. ENVIRON. MICROBIOL. (USA) , 1994, 60/4 (1359-1363)

Three Listeria monocytogenes strains isolated from food or food- processing environments were used to assess the response of this species to salinity in a chemically defined minimal medium. Growth in a minimal medium containing five essential amino acids and glucose as a carbon and energy



source was comparable to growth in a rich medium (brain heart infusion broth). In the absence and presence of 3% NaCl the final cell numbers reached in minimal medium were 109 and 107 CFU/ml, respectively. Growth under the latter conditions could not be detected by spectrophotometry by measuring A660. Apparently, this technique was not suitable for these experiments since the detection level was > 107 CFU/ml. Exogenously added proline (10 mM), trimethylglycine (betaine) (1 mM), and beta-hydroxy-gamma-N-trimethyl aminobutyrate (carnitine) (1 mM) significantly stimulated growth under osmotic stress conditions in minimal medium at both 37 and 10degreeC. Betaine and carnitine are present in foods derived from plants and animals, respectively. Therefore, these compounds can contribute significantly to growth of L. monocytogenes in various foods at high osmolarities.

TOP

Betaine:homocysteine methyltransferase - A new assay for the liver enzyme and its absence from human skin fibroblasts and peripheral blood lymphocytes

Wang J.; Dudman N.P.B.; Lynch J.; Wilcken D.E.L. Department of Medicine, Prince Henry Hospital, Little Bay, NSW 2036 Australia CLIN. CHIM. ACTA (Netherlands) , 1991, 204/1-3 (239-250)

Chronic elevation of plasma homocysteine is associated with increased atherogenesis and thrombosis, and can be lowered by betaine (N,N,N-trimethylglycine) treatment which is thought to stimulate activity of the enzyme betaine:homocysteine methyltransferase. We have developed a new assay for this enzyme, in which the products of the enzyme-catalysed reaction between betaine and homocysteine are oxidised by performic acid before being separated and quantified by amino acid analysis. This assay confirmed that human liver contains abundant betaine:homocysteine methyltransferase (33.4 nmol/h/mg protein at 37degreeC, pH 7.4). Chicken and lamb livers also contain the enzyme, with respective activities of 50.4 and 6.2 nmol/h/mg protein. However, phytohaemagglutinin-stimulated human peripheral blood lymphocytes and cultured human skin fibroblasts contained no detectable betaine:homocysteine methyltransferase (< 1.4 nmol/h/mg protein), even after cells were pre-cultured in media designed to stimulate production of the enzyme. The results emphasize the importance of the liver in mediating the lowering of elevated circulating homocysteine by betaine.

TOP

Antimicrobial activity of betaine esters, quaternary ammonium amphiphiles which

spontaneously hydrolyze into nontoxic components

Lindstedt M.; Allenmark S.; Thompson R.A.; Edebo L. Department of Clinical Bacteriology, University of Goteborg, Guldhedsgatan 10A, S-413 46 Goteborg Sweden ANTIMICROB. AGENTS CHEMOTHER. (USA) , 1990, 34/10 (1949-1954)

A series of quaternary ammonium compounds that are esters of betaine and fatty alcohols with hydrocarbon chain lengths of 10 to 18 carbon atoms were tested with respect to antimicrobial activities and rates of hydrolysis. When the tetradecyl derivatives was tested against some selected microorganisms, the killing effect was comparable to that of the stable quaternary ammonium compound cetyltrimethylammonium bromide. At higher pH values, both the antimicrobial effect and the rate of hydrolysis of the esters increased. However, whereas at pH 6 greater than 99.99% killing of Salmonella typhimurium was achieved with 5 microg/ml in 3 min, the rate of hydrolysis was less than 20% in 18 h. At pH 7, a similar killing effect was achieved in 2 min and 50% hydrolysis occurred in ca. 5 h. Thus, it is possible to exploit the rapid microbicidal effect of the compounds before they hydrolyze. The rate of hydrolysis was reduced by the presence of salt. The bactericidal effect of the betaine esters increased with the length of the hydrocarbon chain of the fatty alcohol moiety up to 18 carbon atoms. Since the hydrolysis products are normal human metabolites, the hydrolysis property may extend the use of these quaternary ammonium compounds as disinfectants and antiseptics for food and body surfaces.

TOP

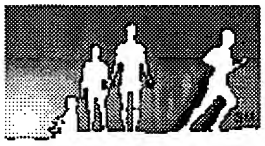
Cardiovascular risk factors in the older adult

Kannel W.B. Hospital Practice (USA) , 1996, 31/11 (135-138+143-144+147-148)

The potential benefits of correcting identified cardiovascular risk factors in the elderly are substantial. Treatment of hypertension has been shown to reduce morbidity and mortality, and correction of dyslipidemia prevents recurrent coronary events. Other measures (e.g., lowering fibrinogen and homocysteine levels, weight reduction) whose efficacy in the elderly has not been established are nevertheless recommended.

TOP

S-nitrosation ameliorates homocysteine-mediated neurotoxicity in primary culture of rat cortical neurons



Kim W.-K. Division of Neuroscience, Medical Research Center, Ewha Womans University, Seoul South Korea Korean Journal of Pharmacology (South Korea) , 1996, 32/2 (169-175)

The reactivity of the sulfhydryl (thiol) group of homocysteine has been associated with an increased risk of atherosclerosis, thrombosis and stroke. Thiols also react with nitric oxide (NO, an endothelium-derived relaxing factor (EDRF)), forming S-nitrosothiols that have been reported to have potent vasodilatory and antiplatelet effects and been expected to decrease adverse vascular effects of homocysteine. The present study was aimed to investigate whether the S-nitrosation of homocysteine modulates the neurotoxic effects of homocysteine. An 18 hour-exposure of cultured rat cortical neurons to homocysteine (>1 mM) resulted in a significant neuronal cell death. At comparable concentrations (<10 mM), however, S-nitrosohomocysteine did not induce neuronal cell death. Furthermore, S-nitrosohomocysteine partially blocked NMDA-mediated neurotoxicity. S-nitrosohomocysteine also decreased NMDA-mediated increases in intracellular calcium concentration. The present data indicate that in brain nitric oxide produced from neuronal and nonneuronal cells can modulate the potential, adverse properties of homocysteine.

TOP

Hyperhomocystinemia threatens patients with kidney failure. Are intravenously administered high dosed vitamins effective?

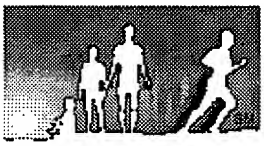
Schmidt K.A. Weinsbergerstrasse 74, D-50823 Koln Germany Fortschritte der Medizin (Germany) , 1996, 114/24 (44-45)

Therapy 0160; Mammal 0738; Human 0888; Intravenous drug administration 0182; Note 0063 DRUG DESCRIPTORS: *vitamin b group--drug therapy--dt; *vitamin b group--drug combination--cb; * vitamin b group--drug administration--ad; *folic acid--drug therapy--dt; *folic acid--drug combination--cb; *homocysteine--endogenous compound--ec; *pyridoxine --drug therapy--dt; *pyridoxine--drug combination--cb; *hydroxocobalamin--drug therapy--dt; *hydroxocobalamin--drug combination--cb MEDICAL DESCRIPTORS: *kidney failure--drug therapy--dt; *homocystinuria; *atherosclerosis drug efficacy; risk factor; human; intravenous drug administration; note

TOP

Homocystinuria: What about mild hyperhomocysteinaemia?

Van den Berg M.; Boers G.H.J. Institute Cardiovascular Research,



Department of Vascular Surgery, Free University Hospital, PO Box 7057, 1007 MB Amsterdam Netherlands Postgraduate Medical Journal (United Kingdom) , 1996, 72/851 (513-518)

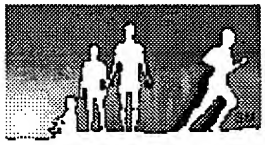
Hyperhomocysteinaemia is associated with an increased risk of atherosclerotic vascular disease and thromboembolism, in both men and women. A variety of conditions can lead to elevated homocysteine levels, but the relation between high levels and vascular disease is present regardless of the underlying cause. Pooled data from a large number of studies demonstrate that mild hyperhomocysteinaemia after a standard methionine load is present in 21% of young patients with coronary artery disease, in 24% of patients with cerebrovascular disease, and in 32% of patients with peripheral vascular disease. From such data an odds ratio of 13.0 (95% confidence interval 5.9 to 28.1), as an estimate of the relative risk of vascular disease at a young age, can be calculated in subjects with an abnormal response to methionine loading. Furthermore, mild hyperhomocysteinaemia can lead to a two- or three-fold increase in the risk of recurrent venous thrombosis. Elevated homocysteine levels can be reduced to normal in virtually all cases by simple and safe treatment with vitamin B6, folic acid, and betaine, each of which is involved in methionine metabolism. A clinically beneficial effect of such an intervention, currently under investigation, would make large-scale screening for this risk factor mandatory.

Top

Plasma homocyst(e)ine levels and graded risk for myocardial infarction: Findings in two populations at contrasting risk for coronary heart disease

Malinow M.R.; Ducimetiere P.; Luc G.; Evans A.E.; Arveiler D.; Cambien F.; Upson B.M. Oregon Regional Primate Research Cen, 505 NW 185th Avenue, Beaverton, OR 97006 USA Atherosclerosis (Ireland) , 1996, 126/1 (27-34)

Standardized mortality rates for coronary heart disease (CHD) in men are about 3-fold higher in Northern Ireland than in France. The differences could not be explained by the presence of conventional risk factors for atherosclerosis. We studied in subjects from these two countries, an additional risk factor, namely, concentration of plasma homocyst(e)ine which is frequently elevated in patients with CHD. We measured the plasma concentration of homocyst(e)ine in survivors of myocardial infarction (MI) and in control subjects from the Belfast, Strasbourg and Lille regions. Plasma homocyst(e)ine levels were higher in the Irish than in the French controls; subjects with MI had higher levels than controls. Results were compatible with global excess of risk for MI being graded across the distribution of plasma homocyst(e)ine concentrations, although the trends

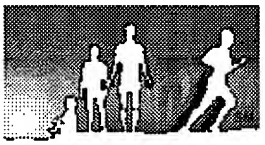


lost significance in Belfast after adjustment for other risk factors. The higher plasma homocyst(e)ine concentrations we observed in the Irish population could be the reason for the different CHD mortality rates. This epidemiological observation could prompt dietary and vitamin supplementation studies aimed at decreasing homocyst(e)ine levels as well as the incidence of arterial occlusive disease, under controlled conditions in high risk populations.

Effect of homocysteine on copper ion-catalyzed, azo compound-initiated, and mononuclear cell-mediated oxidative modification of low density lipoprotein

Halvorsen B.; Brude I.; Drevon C.A.; Nysom J.; Ose L.; Christiansen E.N.; Nenseter M.S. Institute for Nutrition Research, University of Oslo, P.O. Box 1046, Blindern, 0316 Oslo Norway Journal of Lipid Research (USA) , 1996, 37/7 (1591-1600)

Homocysteine is an independent risk factor for cardiovascular diseases. The mechanisms by which elevated plasma concentrations of homocysteine are related to the pathogenesis of atherosclerosis are not fully understood. To examine whether homocysteine is implicated in atherogenesis through the modification of low density lipoprotein (LDL), the effect of homocysteine on the oxidation of LDL was studied by three different oxidation systems. Thus, LDL was subjected to Cu2+-catalyzed, azo compound-initiated, and peripheral blood mononuclear cell-mediated oxidative modification. The extent of modification was assessed by measuring the formation of conjugated dienes, lipid peroxides, thiobarbituric acid-reactive substances, and the relative electrophoretic mobility. Homocysteine at a normal plasma concentration (6 *p) showed no effect, whereas a concentration corresponding to moderate hyperhomocysteinemia (25 microM) or to concentrations seen in homocystinuria patients (100, 250, and 500 microM) protected LDL from modification of the lipid as well as of the protein moiety. One exception was observed: when the oxidation was initiated by copper ions, homocysteine at concentrations 6 and 25 microM stimulated the lipid peroxidation of LDL to a small, but statistically significant extent. High concentrations of homocysteine showed antioxidative properties as long as the thiol groups were intact, thereby delaying the onset of the oxidation. The 1,1-diphenyl-2-picrylhydracyl radical test demonstrated that homocysteine at concentrations less than or equal to50 microM possessed marked free radical scavenging capacity. Finally, LDL isolated from two patients with homozygous homocystinuria showed similar extent of Cu2+-catalyzed oxidation as LDL from a group of healthy control subjects. Taken together, our data suggest that low concentrations of homocysteine in the presence of copper ions may enhance the lipid peroxidation of LDL, whereas high concentrations of homocysteine may protect LDL against oxidative



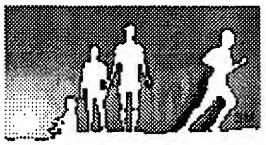
modification in the lipid as well as in the protein moiety. Thus, homocysteine-induced atherosclerosis may be explained by mechanisms other than oxidative modification of low density lipoprotein.

Hyperhomocysteinemia, hyperfibrinogenemia, and lipoprotein (a) excess in maintenance dialysis patients: A matched case-control study

Bostom A.G.; Shemin D.; Lapane K.L.; Sutherland P.; Nadeau M.R.; Wilson P.W.F.; Yoburn D.; Bausserman L.; Tofler G.; Jacques P.F.; Selhub J.; Rosenberg I.H. Jean Mayer USDA, Human Nutrition Res. Center on Aging, Tufts New England Medical Center, 711 Washington Street, Boston, MA 02111 USA Atherosclerosis (Ireland) , 1996, 125/1 (91-101)

Maintenance dialysis patients experience an exceedingly high incidence of arteriosclerotic cardiovascular disease (CVD) events that are poorly predicted by traditional CVD risk factor indices. We evaluated the prevalence of three non-traditional CVD risk factors i.e. hyperhomocysteinemia, hyperfibrinogenemia, and lipoprotein(a) (Lp(a)) excess, and combined hyperhomocysteinemia, hyperfibrinogenemia, and Lp (a) excess, in maintenance dialysis patients. Fasting total plasma homocysteine (Hcy), fibrinogen, Lp(a), glucose, and total and HDL cholesterol levels, and traditional CVD risk factor (i.e. glucose tolerance, smoking, hypertension, dyslipidemia) prevalences were assessed in 71 dialysis patients and 71 age, sex, and race matched Framingham Study controls free of clinical renal disease, with normal serum creatinine (less than or equal to 1.5 mg/dl). Mean plasma Hcy (23.7 vs. 9.9 microM, P = 0.0001), fibrinogen (457 vs. 309 mg/dl, P = 0.0001), and Lp(a) (30 vs. 17 mg/dl, P = 0.0070) levels were substantially increased in the dialysis patients. Matched odds ratios (with 95% confidence intervals), dialysis patients/controls, for hyperhomocysteinemia, hyperfibrinogenemia, and Lp (a) excess, alone or combined, were markedly greater in the dialysis patients, with no evidence of confounding by the traditional CVD risk factors; hyperhomocysteinemia, 105.0 (29.9 368.9); hyperfibrinogenemia, 16.6 (6.6 42.0) Lp(a) excess, 3.5 (1.5-8.4); all three combined 35.0 (5.7 199.8). Given in vitro evidence that Hcy, Lp(a), and fibrinogen interact to promote atherothrombosis, combined hyperhomocysteinemia, hyperfibrinogenemia, and Lp(a) excess may contribute to the high incidence of vascular disease sequelae experienced by dialysis patients, which is inadequately explained by traditional CVD risk factors. Controlled, prospective studies of well-characterized maintenance dialysis cohorts are urgently required to substantiate this hypothesis.

Prevalence of familial mild



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hyperhomocysteinemia

Franken D.G.; Boers G.H.J.; Blom H.J.; Cruysberg J.R.M.; Trijbels F.J.M.; Hamel B.C.J. Department of Radiology, University Hospital Nijmegen, Post Box 9101, 6500 HB Nijmegen Netherlands Atherosclerosis (Ireland) , 1996, 125/1 (71-80)

Previous studies have shown that elevated basal homocysteine levels are correlated among family members of patients with coronary vascular disease and juvenile venous thrombosis. This suggests the possibility of the presence of inherited basal mild hyperhomocysteinemia (mHH). We studied homocysteine levels, fasting as well as after methionine load, among 96 family members of 21 post-load hyperhomocysteinemic vascular index patients, i.e. 6 parents, 27 offspring, 38 siblings, 19 uncles and aunts and 6 cousins. In 15 out of 21 screened families post-load mHH was established in at least one family member. Fasting and post-load mHH was observed in 19 out of 89 (21%) screened family members (fasting homocysteine levels not measured in seven family members), and 31 out of 96 screened family members (32%), respectively. In 40% of all family members, post-load mHH was not accompanied by fasting mHH. We conclude that both fasting and post-load mHH seems to be inherited in the majority of hyperhomocysteinemic vascular patients.

Top

Thrombosis and systemic lupus erythematosus: The hopkins lupus cohort perspective

Petri M. Division of Rheumatology, John Hopkins University, School of Medicine, 1830 E. Monument Street, Baltimore, MD 21205 USA Scandinavian Journal of Rheumatology (Norway) , 1996, 25/4 (191-193)

Vascular damage in systemic lupus erythematosus (SLE) occurs through vasculitis, premature atherosclerosis, and hypercoagulability (predominantly due to the antiphospholipid antibody syndrome). In the Hopkins Lupus Cohort, a prospective cohort study, the incidence of thrombosis is 2 per 100 person-years of follow-up. Markers of immune-complex mediated injury (high anti-dsDNA and low C3), atherosclerosis (hypertension, hyperlipidemia, homocysteine) and antiphospholipid antibodies (lupus anticoagulant or anticardiolipin) are independent predictors of thrombosis. Hydroxychloroquine use is protective against future thrombosis.

Top

Risk factors related to carotid intima-media thickness and plaque in children with familial hypercholesterolemia and control subjects

Tonstad S.; Joakimsen O.; Stensland-Bugge E.; Leren T.P.; Ose L.; Russell D.; Bonaa K.H. Lipid Clinic, Rikshospitalet, N-0027 Oslo Norway Arteriosclerosis, Thrombosis, and Vascular Biology (USA) , 1996, 16/8 (984-991)

To assess the relationship between risk factors for cardiovascular disease and early atherosclerotic changes in the carotid artery, we measured carotid intima-media thickness by B-mode ultrasonography in 61 boys and 29 girls 10 to 19 years old with familial hypercholesterolemia (FH) and 30 control subjects matched for age and sex. All were nonsmokers, and all the FH adolescents had a known mutation in the LDL receptor gene. Mean intima-media thickness in the far wall of the carotid bulb was greater (P=.03) in the FH group than in the control subjects: 0.54 mm (95% confidence interval (CI), 0.52 to 0.56) versus 0.50 mm (95% CI, 0.47 to 0.52). In the entire group, mean and maximum intima-media thicknesses in the carotid bulb were positively associated with levels of apolipoprotein B and fibrinogen after control for pubertal stage (r=.19 to .24; P<.05), as was male sex. Plasma total homocysteine was similar in the FH and control groups and was associated with mean and maximum intima-media thicknesses in the far wall of the common carotid artery and carotid bulb after control for pubertal stage (r=.22 to .28; P<.05). With the exception of the relation between plasma fibrinogen level and mean carotid bulb intima-media thickness, these associations were essentially unchanged in stepwise multiple linear regression analyses, allowing for the entry of BMI and level of HDL cholesterol into the analysis. Carotid artery plaque was present in 10% of the children with FH versus none of the control subjects. Children with plaque had a higher mean cholesterol-years score than children without plaque. These findings suggest that the classic lipid and hemostatic risk factors as well as plasma total homocysteine are associated with markers of early carotid atherosclerosis from the second decade of life. B-mode ultrasonography may prove to be a useful tool in risk stratification of children with FH.

TOP

Vascular dysfunction in monkeys with diet-induced hyperhomocyst(e)inemia

Lentz S.R.; Sobey C.G.; Piegors D.J.; Bhopatkar M.Y.; Faraci F.M.; Malinow M.R.; Heistad D.D. Department of Internal Medicine, University of Iowa, Iowa City, IA 52242 USA Journal of Clinical Investigation (USA) , 1996, 98/1 (24-29)

Elevated plasma homocyst(e)ine may predispose to complications of vascular disease. Homocysteine alters vasomotor regulatory and anticoagulant properties of cultured vascular endothelial cells, but little is known about effects of hyperhomocyst(e)inemia on vascular function in vivo. We tested the hypothesis that diet-induced moderate hyperhomocyst(e) inemia is associated with vascular dysfunction in cynomolgus monkeys.

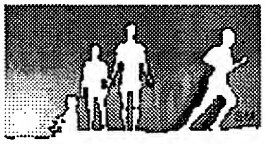
Plasma homocyst(e)ine increased from 4.0plus or minus0.2 microM when monkeys were fed normal diet to 10.6plus or minus2.6 microM when they were fed modified diet (meanplus or minusSE; P = 0.02). Vasomotor responses were assessed in vivo by quantitative angiography and Doppler measurement of blood flow velocity. In response to activation of platelets by intraarterial infusion of collagen, blood flow to the leg decreased by 42plus or minus9% in monkeys fed modified diet, compared with 14plus or minus11% in monkeys fed normal diet (P = 0.008). Responses of resistance vessels to the endothelium-dependent vasodilators acetylcholine and ADP were markedly impaired in hyperhomocyst(e)inemic monkeys, which suggests that increased vasoconstriction in response to collagen may be caused by decreased vasodilator responsiveness to platelet-generated ADP. Relaxation to acetylcholine and, to a lesser extent, nitroprusside, was impaired ex vivo in carotid arteries from monkeys fed modified diet. Thrombomodulin anticoagulant activity in aorta decreased by 34plus or minus15% in hyperhomocyst(e)inemic monkeys (P = 0.03). We conclude that diet-induced moderate hyperhomocyst(e)inemia is associated with altered vascular function.

TOP

Hyperhomocysteinemia induced by folic acid deficiency and methionine load - Applications of a modified HPLC method

Durand P.; Fortin L.J.; Lussier-Cacan S.; Davignon J.; Blache D. INSERM CJF 93-10, Lab. de Biochimie des Lipoproteines, Universite de Bourgogne, 7 bd Jeanne d'Arc, 21033 Dijon Cedex France Clinica Chimica Acta (Netherlands) , 1996, 252/1 (83-93)

The increasing possibility that homocysteine might be involved in atherosclerosis in non-homocysteinuric subjects has required the measurement of low concentrations of this aminothiol in biological samples. The procedure described here represents an improvement of different HPLC methods. We utilized an isocratic HPLC system with fluorescence detection of plasma total homocysteine derivatized after reaction with ammonium 7-fluoro-benzo-2-oxa-1,3- diazole-4-sulphonate. With the help of the rapidly eluting internal standard N-acetyl-cysteine, the method ensures very good recovery (similar100%), reproducibility and precision (within-assay: 2.31%; day-to-day: 2.8%) in the physiological concentration range. This procedure allowed us to validate various animal models of hyperhomocysteinemia such as dietary folic acid deficiency in rat and acute methionine loads in rat and hamster. Using this method, we also confirmed that men have higher plasma total homocysteine levels than women. Due to its simplicity and reliability, our procedure is suitable for routine analysis of total homocysteine and other aminothiols (cysteine, cysteinyl-glycine and glutathione) in biological samples, as required in clinical and research laboratories.



Dietary methionine imbalance, endothelial cell dysfunction and atherosclerosis

Toborek M.; Hennig B. Dept. of Nutrition and Food Science, University of Kentucky, Lexington, KY 40506-0054 USA Nutrition Research (USA) , 1996, 16/7 (1251-1266)

Dietary factors can play a crucial role in the development of atherosclerosis. High fat, high calorie diets are well known risk factors for this disease. In addition, there is strong evidence that dietary animal proteins also can contribute to the development of atherosclerosis. Atherogenic effects of animal proteins are related, at least in part, to high levels of methionine in these proteins. An excess of dietary methionine may induce atherosclerosis by increasing plasma lipid levels and/or by contributing to endothelial cell injury or dysfunction. In addition, methionine imbalance elevates plasma/tissue homocysteine which may induce oxidative stress and injury to endothelial cells. Methionine and homocysteine metabolism is regulated by the cellular content of vitamins B6, B12, riboflavin and folic acid. Therefore, deficiencies of these vitamins may significantly influence methionine and homocysteine levels and their effects on the development of atherosclerosis.

Homocysteine induced arteriosclerosis-like alterations of the aorta in normotensive and hypertensive rats following application of high doses of methionine

Matthias D.; Becker C.-H.; Riezler R.; Kindling P.H. AG Zytopathologie, Haus 55, B.-Buch, Robert-Rossle-Str. 10, D-13125 Berlin Germany Atherosclerosis (Ireland) , 1996, 122/2 (201-216)

Following oral administration of methionine in high doses to normotensive (NR) and spontaneously hypertensive (SHR) rats, its degradation product, homocysteine (HC), which is markedly elevated in serum, exerts an angiotoxic action directed to the aorta. This is accompanied by considerable loss of endothelium and degeneration, partly with dissolution of the media cells with formation of characteristic processes of the degenerating mitochondria, and by elevated HC and cystathion (CT) values in the aortic wall. At the arterial vessels of other organs similar alterations did not occur. There are quantitative differences between NR and SHR. In SHR, serum shows higher HC and CT concentrations than in NR, and the methionine-related aortic alterations are considerably more pronounced and develop earlier, with the additional formation of connective tissue. Here, a certain dependence on the methionine dose is noted, in contrast to NR, for which the

magnitude of the reaction appears to be more related to the length of time of methionine application. Additional administration of atherogenic substances (cholestane-3beta,5alpha,6beta-triol, cholesterol, angiotensin II, cholic acid with methylthiouracil) in SHR causes an exacerbation of the methionine-related aortic alterations. Only cholestane-triol has the same effect on the aortic wall in NR and SHR, with more accentuation in SHR. Cholestane-triol has, in NR as well as in SHR, a high coincidence with methionine-induced morphological reactions including the formation of mitochondrial processes. Simultaneous application of these two substances did not cause a potentiation of the effect. High doses of cholesterol bring about aortic alterations in SHR but not in NR. Thus, in addition to the disorder of fat and carbohydrate metabolism, disturbed protein metabolism is of decisive importance as a risk factor for coronary and other vascular diseases.

TOP

Increased serum level of total homocysteine in CAPD patients: Despite fish oil therapy

Holdt B.; Korten G.; Knippel M.; Lehmann J.K.; Claus R.; Holtz M.; Hausmann S. Universitat Rostock, Klinik fur Innere Medizin, 18059 Rostock Germany Peritoneal Dialysis International (Canada) , 1996, 16/SUPPL. 1 (S246-S249)

It has been shown that serum total homocysteine (HC) is a risk factor for vascular disease which characterizes endothelial damage. The incidence of vascular disease is increased in continuous ambulatory peritoneal dialysis (CAPD) patients. Our aim was to investigate: (1) whether concentration of HC correlates with atherosclerotic and inflammatory events, and (2) if fish oil therapy can retard the disturbance In lipid metabolism which promotes atherosclerosis. Fourteen patients with various degrees of impaired peritoneal clearance and lipid metabolism were observed. In all patients the serum HC was elevated. Seven patients were treated with fish oil for three months. The results indicate an average increase of HC (+18%), total cholesterol (+6.6%), aggregation of erythrocytes (+9%), and an average decrease of dialysate-to-plasma creatinine (D/P) ratio (-7%), deformability of erythrocytes (-8%), and normalization of elevated soluble interleukin-2 receptor (sIL-2R) values. Regression analysis of all data demonstrated a significant correlation between HC and parameters of lipid metabolism and hemorheology. There were no significant correlations between HC and peritoneal function and serum cytokine levels. We conclude that the treatment in CAPD patients with fish oil did not improve the lipid metabolism disturbances in atherosclerosis and peritoneal function. Elevated HC confirms the progression of the disease.

TOP

Hamocysteine antagonism of nitric oxide-

related cytostasis in Salmone la typhimurium

De Groote M.A.; Testerman T.; Xu Y.; Stauffer G.; Fang F.C. Department of Medicine, Univ. Colorado Health Sciences Ctr., Denver, CO 80262 USA Science (USA) , 1996, 272/5260 (414-417)

Nitric oxide (NO) is associated with broad-spectrum antimicrobial activity of particular importance in infections caused by intracellular pathogens. An insertion mutation in the metL gene of Salmonella typhimurium conferred specific hypersusceptibility to S-nitrosothiol NO-doner compounds and attenuated virulence of the organism in mice. The metL gene product catalyzes two proximal metabolic steps required for homocysteine biosynthesis. S-Nitrosothiol resistance was restored by exogenous homocysteine or introduction of the metL gene on a plasmid. Measurement of expression of the homocysteine-sensitive metH gene indicated that S-nitrosothiols may directly deplete intracellular homocysteine. Homocysteine may act as an endogenous NO antagonist in diverse processes including infection, atherosclerosis, and neurologic disease.

Homocysteine, folate, and vascular disease

Kannel W.B.; Wilson P.W.F. Framingham Heart Study, Boston University School of Medicine, Boston, MA USA Journal of Myocardial Ischemia (USA) , 1996, 8/2 (60-63)

Current evidence indicates that the genesis of atherosclerotic disease is multifactorial. One of the newly recognized factors that contributes to this process is raised homocysteine blood levels. A variety of atherosclerotic processes may be facilitated by elevated homocysteine levels, including stimulation of smooth muscle cell growth, impairment of endothelial regeneration, oxidation of LDL particles, and thrombogenesis. A generic defect may account for some instances of hyperhomocysteinemia, but the majority of persons with high levels do not have known genetic defects to account for their elevations. Low levels of folic acid, vitamin B12, and pyridoxine appear to underlie most cases of elevated homocysteine levels. Adding folic acid to the diet may reduce homocysteine levels, but a link between increasing folic acid and lower risk of atherosclerotic disease has yet to be demonstrated in clinical trials. However, increasing daily folic acid intake is not unjustified in some patients. Since this may mask B12 deficiency, a supplement of cobalamin, 1 mg/d has been proposed. In the final analysis, a clinical trial is needed to determine the true significance of hyperhomocysteinemia. Meanwhile, physicians and patients can consider increasing the daily folate intake by eating more oranges, leafy vegetables, wheat products, and cereals.

Ischemic heart disease

Williams J.P. Department of Anesthesiology, UCLA School of Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90095 USA Current Opinion in Anaesthesiology (United Kingdom) , 1996, 9/ (21-26)

Much has changed in the field of myocardial i. :hemia over the past 3 years. The central assumption that coronary artery di .ease is synonymous in men and women is under revision. Increasingly, the medical community is recognizing the importance of an altered presentation of the myocardial ischemic syndrome in women. Indeed, the very definition of ischemia itself is under revision. There is mounting evidence that ischemia requires a two-stage definition: the first for biochemical evid nce and the second for physiological. The method by which one mak s the diagnosis of ischemia is also constantly being reviewed. The use of Ho er monitoring for ischemic diagnosis is still a topic for debate. Specificall , whether to use two or three leads and where those leads should be placed remains controversial. In fact, there is some question now as to not only the importance of silent ischemia but also whether all angina is ischemia. There is evidence to suggest that some angina is only memory. The traditional epidemiological view of coronary atherosclerotic risk factors is also under review and refinement. An accelerated rate of decline in ventilatory funct r, lactose tolerance, and serum levels of homocysteine are some of the w epidemiological risk factors that are touted as equal or superior to t e traditional ones for predicting long-term mortality and morbidity. And what of the role of inflammation in triggering thrombosis and plaque rupture? Is the incidence of thrombosis the same wherever an atherosclerotic plaque occurs? Is fibrinogen an important risk factor? This revie v will briefly examine the new findings in each of these areas and discus the relevant material where appropriate.

Homocysteine and hemostasi : Pathogenetic mechanisms predisposing to hrombosis

Harpel P.C.; Zhang X.; Borth W. Box 1079, 1 Gustave Levy Place, New York, NY 10029 USA Journal of Nutrition (U A) , 1996, 126/4 SUPPL. (1285S-1289S)

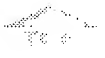
Growing evidence suggests that moderately elevated levels of homocyteine are associated not only with arterial thrombosis and atherosclerosis but also with venous thrombosis as well. We have revi wed recent studies that indicate that homocysteine inhibits several dif erent anticoagulant mechanisms that are mediated by the vascular endothelium. The protein C enzyme system appears to be one of the most i portant anticoagulant pathways in the blood. Homocysteine inhibits e expression and activity of endothelial cell surface thrombomodulin, the t rombin cofactor responsible for protein C activation. Homocysteine inhibits the antithrombin III binding

activity of endothelial heparan sulfate proteoglycan, thereby suppressing the anticoagulant effect of antithrombin III. Homocysteine also inhibits the ecto-ADPase activity of human umbilical vein endothelial cells (HUVECS). Because ADP is a potent platelet aggregatory agent, this action of homocysteine is prothrombotic. Homocysteine also interferes with the fibrinolytic properties of the endothelial surface because it inhibits the binding of tissue plasminogen activator. Homocysteine stimulates HUVEC tissue factor activity. We have found that lipoprotein(a) (Lp(a)) also stimulates HUVEC tissue factor activity. The combination of Lp(a) plus homocysteine induced more tissue factor activity than either agent alone. These disruptions in several different vessel wall-related anticoagulant functions provide plausable mechanisms for the occurrence of thrombosis in hyperhomocysteinemia.

Homocysteine and coronary atherosclerosis

Mayer E.L.; Jacobsen D.W.; Robinson K. Department of Cardiology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195 USA Journal of the American College of Cardiology (USA) , 1996, 27/3 (517-527)

Homocysteine is increasingly recognized as a risk factor for coronary artery disease. An understanding of its metabolism and of the importance of vitamins B6 and B12 and folate as well as enzyme levels in its regulation will aid the development of therapeutic strategies that, by lowering circulating concentrations, may also lower risk. Possible mechanisms by which elevated homocysteine levels lead to the development and progression of vascular disease include effects on platelets, clotting factors and endothelium. This review presents the clinical and basic scientific evidence supporting the risk and mechanisms of vascular disease associated with elevated homocysteine concentrations as well as the results of preliminary therapeutic trials.



The effect of reduced glomerular filtration rate on plasma total homocysteine concentration

Arnadottir M.; Hultberg B.; Nilsson-Ehle P.; Thysell H. Department of Medicine, National University Hospital, 101 Reykjavik Iceland Scandinavian Journal of Clinical and Laboratory Investigation (Norway) , 1996 , 56/1 (41-46)

The concentration of homocysteine in plasma has been shown to be increased in renal failure, possibly contributing to the accelerated atherosclerosis observed in uraemic patients. The aim of the present study

was to document the relationship between plasma total homocysteine (tHcy) concentrations and glomerular filtration rates (GFR) in highly selected patients, with renal function ranging from normal to dialysis dependency. GFR was defined as the plasma clearance of iohexol; a more accurate method than the creatinine-based estimations applied in previous studies. Plasma tHcy concentrations were highly correlated to GFR ($r=0.70$, $p<0.0001$) and were significantly increased already in moderate renal failure. According to a multiple regression analysis, GFR and red cell folate concentrations independently predicted plasma tHcy concentrations, whereas those of serum creatinine, plasma pyridoxal-5-phosphate, urine albumin and urine alpha-1-microglobulin (a marker of tubular damage) did not. Thus, GFR seems to be a better determinant of plasma tHcy concentration than serum creatinine concentration. Plasma total cysteine and total cysteinylglycine concentrations followed the same pattern as those of tHcy.

Lack of effect of oral N-acetylcysteine on the acute dialysis-related lowering of total plasma homocysteine in hemodialysis patients

Bostom A.G.; Shemin D.; Yoburn D.; Fisher D.H.; Madeau M.R.; Selhub J. Vitamin Bioavailability Laboratory, J.Mayer USDA Human Nutrit. Res. Ctr., Tufts New England Medical Center, 711 Washington Street, Boston, MA 02111 USA Atherosclerosis (Ireland), 19 , 120/1-2 (241-244)

Hyperhomocysteinemia refractory to standard B-vitamin supplementation treatment persists in greater than or equal to 7. . f maintenance dialysis patients, potentially increasing their risk for atherothrombotic sequelae. We examined whether predialysis administration of oral N-acetylcysteine (NAC), which acutely increases the non-protein bound, dialyzable fraction of plasma homocysteine, might augment the homocysteine-lowering effect of dialysis therapy. Predialysis and postdialysis total plasma homocysteine levels were determined on a control day, and on a day in which oral NAC (1200 mg) was administered predialysis in 11 maintenance hemodialysis patients. Although NAC treatment had no significant effect on hemodialysis removal of plasma homocysteine ($P = 0.594$), we observed a 16% reduction ($P = 0.033$) in non-fasting prehemodialysis total plasma homocysteine on the NAC treatment vs. non-treatment day. Longer-term, placebo-controlled confirmation of this finding will be required to evaluate the possible chronic homocysteine-lowering efficacy of NAC treatment in hemodialysis patients.

Homocysteine: Relation with ischemic vascular diseases

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Homocysteine, a sulfur-containing amino acid. is an intermediate metabolite of methionine. Patients with homocystinuria a d severe hyperhomocysteinemia develop premature arte iosclerosis and arterial thrombotic events, and venous thromboemboli m. Studies suggest that moderate hyperhomocysteinemia can be consi ered as an independent risk factor in the development of premature cardio ascular disease. In vitro, homocysteine has toxic effects on endothelial ells. Homocysteine can promote lipid peroxidation and damage vascu r endothelial cells. Moreover, homocysteine interferes with the natural antic gulant system and the fibrinolytic system. Homocysteinemia should : known in patients with premature vascular diseases, especially in subj ts with no risk factors. Folic acid, vitamin B6 can lower homocysteine leve s.

Hyperhomocysteinemia: Bac ground, diagnosis and treatment

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Hyperhomocysteinemia is a disorder of the m hionine metabolism, which is accompanied by elevated blood homocysteine . els. An increasing number of diseases - such as atherosclerosis, thrombos and obstetric complications - is found to be associated with hyperhomocys inemia. Over the last years, also the concept of 'hyperhomocysteinemia' its lf has been changed. Hyperhomocysteinemia is nowadays not syno vmous with heterozygous cystathionine synthase deficiency anymore, bu it is a summary term of an elevated homocysteine level due to any cause. his conceptual change leads to changes in diagnosis and treatment. Becaus there are no data on clinical trials in the field of hyperhomocysteinemia w ommend to perform a methionine loading test only in patients with v cular disease or thrombosis, without other known causes. In the case of hy homocysteinemia one can give the patient the benefit of the doubt and pr scribe a vitamin supplement. First choice therapy might be folic acid (after clusion of vitamin B12 deficiency) whether or not in combination wit vitamin B6.

BACK to the Previous age